REMARKS

Claims 29-45 and 47 stand rejected on the basis that the subject matter of these claims are allegedly not enabled by the specification, with the Examiner taking the position that there is insufficient evidence of record to support a conclusion that the claimed peptide sequence is useful in inhibiting HIV entry into cell *in vivo*. While the Examiner has raised various bases in support of the § 112 rejection, the Examiner's principal underlying concern is that while the specification is admittedly enabling for *in vitro* inhibition of HIV infection, there is allegedly insufficient evidence that the claimed peptides would be useful clinically in *in vivo* therapy. While Appellants continue to contend that the evidence of record is sufficient to demonstrate the utility and enablement of the invention as claimed, additional evidence is herewith submitted which further demonstrates both enablement and utility for the use of the claimed peptide sequence in the treatment of HIV.

In this regard, the Appellants enclose the declaration of Dr. Pramod Nehete, a co-inventor of the subject matter of the pending claims. The Nehete declaration presents the results of animal studies conducted with a peptide covered by the pending claims that contains the so-called R15K sequence. These studies show that the peptide successfully and convincingly inhibited the entry of HIV into cells using an art-accepted SHIV-rhesus model.

In particular, the Nehete declaration provides the following information and evidence:

1. The results of various *in vitro* studies carried out by using accepted *in vitro* systems for testing for treatments useful in HIV treatment, published in Nehete *et al.* (Exhibit 2 to the declaration), demonstrate that the central 15-21 amino acids in the V3 region of gp120 play an important role in HIV infection of $CD4^+$ cells. Peptides from this region bind to target host

cells and inhibit the cellular entry of phenotypically distinct HIV-1 strains. Further, competition for peptide binding was observed with viral particles, but not with recombinant gp120, sCD4, β-chemokines or an antibody to CXCR-4. (See paragraph 2 of the Nehete Declaration)

2. The use of a synthetic peptide-based anti-HIV therapeutic has been validated by a recent report, Kilby *et al.* (Exhibit 3 to the declaration) which reports the results of a clinical trial in human HIV patients wherein potent suppression of HIV load in patients was observed following intravenous administration of T-20, a peptide corresponding to the oligomerization domain of the HIV-1 gp41 transmembrane protein. Subsequently, T-20 has also been successfully tested for subcutaneous administration in humans (unpublished studies). (See paragraph 3 of the Nehete declaration)

3. Using the SHIV-rhesus model, Drs. Nehete and Sastry investigated the therapeutic potential of the V3 peptide R15K, exhibiting anti-HIV activity, by using the protocol described for the foregoing clinical trial with the T-20 peptide in Kilby *et al.*. In this model, infection of rhesus macaques with a chimeric virus, SHIV consisting of SIV core and HIV envelope sequences leads to a productive infection followed by severe loss of CD4 cells and AIDS-related pathology. Thus, in the SHIV-rhesus model, the rhesus macaques are exposed to acute infection by SHIV as opposed to the chronic HIV infection targeted in the human clinical trial using T-20 as the anti-HIV therapeutic reagent.

In paragraphs 4A through 4C of the Nehete declaration, the study protocol and results obtained are described as follows:

-- Two groups of two monkeys each were selected for the study. One group, referred to as control, received daily intravenous infusions of sterile saline (1 ml/dose/animal) for

a total of 15 days. The second group of monkeys received the R15K peptide daily by the intravenous route (60mg in 1 ml/dose/monkey). On day two of the infusions, all four monkeys were challenged with the pathogenic $SHIV_{ku2}$ by the intravenous dose (1 ml containing 1000 $TCID_{50}$). At several days post-challenge, blood samples were collected from each of the animals for determining the viral load by analyzing the plasma samples by using the real-time RT-PCR methodology.

-- The data from the control and treated groups of animals is shown in the Fig.1 (Exhibit 4 of the declaration) as an average for the monkeys in each group. The time scale used is the number of days after viral infection, and therefore, the peptide treatment for the days prior to viral challenge is referred to as days with negative numbering. The differences in the viral loads between the control and treated groups of monkeys is shown both as RNA copy equivalents in either one micro-liter of the plasma (panel on the left) or 1 ml of the plasma after log-transformation (right-side panel). Further, the decrease in viral load in the R15K-treated monkeys is also shown in Fig.2 after log-transformation of the data in RNA copy equivalents.

-- Dr. Nehete reports that the results demonstrate that the viral load is reduced in the R15K-treated monkeys, and the decrease reached a maximum of 1.715 log_{10} units of RNA copy equivalents by day 19 post-challenge (Fig. 2) (Exhibit 4 of the declaration).

Dr. Nehete also provides support for the conclusion that the SHIV-rhesus monkey model is an art-accepted model for predicting clinical efficacy of HIV therapeutics. In particular, in paragraph 5 of the declaration Dr. Nehete states that the SHIV-rhesus monkey model used in the foregoing studiesto demonstrate efficacy of the R15K peptide in the treatment of HIV infections is a model that is accepted by those of skill in the art of testing for HIV therapeutics. This model

has been relied upon frequently in the scientific literature and shown to be a useful model for predicting efficacy of HIV vaccines. See, for example, the articles of I.M. Belyakou et al., H.L. Robinson et al., and N. H. Varouch et al., each attached as Exhibit 5 to the Nehete declaration. Dr. Nehete concludes that using this accepted model, as discussed above, the R15K peptide has been shown to be useful in significantly reducing viral load in infected individuals.

CONCLUSION

It is submitted that this additional evidence provides still further support from which to conclude that the subject matter of the pending claims is enabled and has utility. In light of the foregoing, Appellants respectfully submit that the § 112 rejections have been obviated. As such, the Examiner is requested to reconsider and withdraw the currently pending § 112 rejections and reconsider the one remaining prior art rejection. Should the Examiner have any questions regarding this submission, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

David L. Parker
Reg. No. 32,165

FULBRIGHT & JAWORKSI LLP.
600 Congress Ave., Suite 2400
Austin, Texas 78735
(512) 536-3055

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